

Oxygen

Ravi Taneja FFARCSI FRCA

Ralph S Vaughan FRCA

Key points

Oxygen is a paramagnetic gas

A decrease in PaO₂ from an initially high level has little effect on O₂ content or saturation, whereas a similar fall in PaO₂ in the middle range has a striking effect

Maintenance of supra-normal oxygen delivery is not beneficial in critically ill patients

Oxygen toxicity occurs mainly through the effects of superoxide anion and the hydroxyl free radical

Hypoxia should never be tolerated through a fear of oxygen toxicity

The feeling of it (oxygen) to my lungs was not sensibly different from that of common air; but I fancied that my breast felt peculiarly light and easy for some time afterwards. Who can tell that, in time, this pure air may become a fashionable article in luxury. Hitherto, only two mice and myself have had the privilege of breathing it.

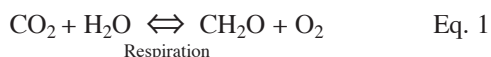
Joseph Priestley, 1775

Priestley, a liberal minister, had endeavoured to extract air from mercuric oxide and was surprised to find that a candle burned in this air much more vigorously than it did in nitrous oxide, the laughing gas he had discovered recently. He called it 'dephlogisticated air', in terms of the then prevalent theory of combustion. Later, this eminently respirable air was found to react with metals and produce acids and erroneously acquired the name 'oxygen' (derived from the Greek terms *oxy* and *genomae* meaning sour and I produce). Ironically, it was Scheele, a pharmacist in Sweden, who had actually discovered oxygen before Priestley and apparently was the first to characterise it. However, Scheele's paper was delayed with the publishers for almost two years, by which time the first public announcement for the discovery of oxygen had been made.

Occurrence and properties

Our knowledge regarding the evolution of oxygen remains mostly speculative. It is thought that when the earth was formed 4.5×10^9 years ago, the atmosphere was predominantly hydrogen and helium. The biosphere was formed as a result of gradual loss of hydrogen and an acquired capacity to produce oxygen via photosynthesis, an obligatory skill of all plant life.

Photosynthesis



Respiration

To date, the precise kinetics of the removal

Table 1 Physicochemical properties of oxygen

Atomic number	8
Atomic weight	15.9994
Melting point	-218.4°C
Boiling point	-183°C
Density	1.429 g l ⁻¹ (1 atm, 0°C)
Valence	2
Electronic configuration	2-6 or 1s2s2p4

of 4 electrons from water to release molecular oxygen remains dismally elusive.

Oxygen is the most prevalent element in the earth's crust with an atom abundance of 53.8%. Most is combined in the form of silicates, water and oxides. It is a colourless and tasteless gas, denser than air and only slightly soluble in water. It is a poor conductor of heat and electricity and supports combustion but does not burn. Normal atmospheric oxygen is a diatomic gas with a molecular weight of 31.9988. When cooled below its boiling point (Table 1), oxygen becomes a pale blue liquid and eventually solidifies, retaining its colour. It is paramagnetic (*i.e.* attracted into a magnetic field) in its solid, liquid and gaseous forms and although eight isotopes are known, atmospheric oxygen is a mixture of the three isotopes with mass numbers 16 (commonest), 17 and 18. It is extremely active chemically, forming compounds with almost all elements except inert gases.

Oxygen transport

Body tissues do not possess a capacity to store oxygen. Thus, cell homeostasis and integrity are critically dependent on the transport of oxygen to the mitochondrion where it is used to generate ATP (adenosine triphosphate). The steps by which PO₂ decreases from air to mitochondria are known as the 'oxygen cascade' and have immense clinical implications as derangements at any step may result in

Ravi Taneja FFARCSI FRCA

Specialist Registrar, Department of Anaesthesia and Intensive Care, University Hospital of Wales, Heath Park, Cardiff CF14 4XW

Ralph S Vaughan FRCA

Consultant, Department of Anaesthesia and Intensive Care, University Hospital of Wales, Heath Park, Cardiff CF14 4XW

Table 2 Oxygen uptake in the lungs

Steps in oxygen cascade	Factors influencing oxygenation
Uptake by lungs	
Inspired gas (P_{iO_2})	F_{iO_2} , barometric pressure
Alveolar gas (P_{AO_2})	V_A , $\dot{V}O_2$
Arterial blood (P_{aO_2})	V/Q ratio, Q_s/Q_t
Alveolar ventilation \dot{V}_D/\dot{V}_T	
Carrying capacity of blood	Haemoglobin, solubility in blood
Delivery from lung to tissues	Cardiac output (regional blood flow) Oxygen saturation, haemoglobin
Cellular use of oxygen	Diffusion from capillary to cell Regional variations in blood flow Mitochondrial integrity

hypoxia. The main facets of oxygen carriage are uptake of oxygen by the lungs and delivery to organs and tissues.

Oxygen uptake in the lungs

Oxygen uptake in the lungs is determined by inspired oxygen concentration, barometric pressure, alveolar ventilation, diffusion capacity and ventilation-perfusion (\dot{V}_A/\dot{Q}) matching (Table 2). Dry air at sea level normally contains 20.9% oxygen, equivalent to a partial pressure of 159 mmHg (21.2 kPa). The partial pressure of oxygen in the alveolar spaces is distinctly lower (110 mmHg, 14.7 kPa) a composite result of alveolar ventilation and dilution by carbon dioxide, water vapour and oxygen consumption. Partial pressures of oxygen in arterial blood are similar and the alveolar-arterial gradient of oxygen (normally < 1 kPa) commonly reflects regional \dot{V}_A/\dot{Q} mismatch rather than diffusion across thin pulmonary capillaries. Further drops in partial pressures of oxygen take place on account of the 'true shunt' (mixed venous blood that bypasses the pulmonary capillary bed).

Inert gases, such as nitrogen and argon, are carried only in the dissolved form in the blood. Oxygen differs from inert gases because of its affinity to haemoglobin (Hb). The Hb molecule consists of four haem molecules combined to a globin molecule. Each haem molecule contains an iron in the ferrous form that has the capacity to bind with one oxygen molecule in a loose reversible combination. Binding of an O_2 molecule to one haem site increases the affinity for ligands at other haem sites on the molecule and the consequent sigmoid shaped constant-pressure relationship is known as the oxyhaemoglobin dissociation curve. Some confusion exists over the oxygen-combining capacity of haemoglobin. It was following the precise measurement of the molecular weight of haemoglobin that the theoretical value of 1.39 ml g^{-1} was derived and used widely. However, this value was not obtained when direct measurements of

haemoglobin concentration and oxygen carrying capacity were compared. Since some iron in haemoglobin may exist as haemochromogens, a value of 1.31 ml g^{-1} has been proposed. The oxygen content of arterial blood may be represented as (Equation 2):

$$Ca_{O_2} = (1.31 \times Hb \times Sa_{O_2}) + 0.003 \times Pa_{O_2}$$

ml dl⁻¹ ml g⁻¹ g dl⁻¹ %/100 ml dl⁻¹ mmHg⁻¹ mmHg

$$19 = (1.31 \times 14.7 \times 0.97) + 0.3$$

The shape and position of the curve has several important physiological consequences:

1. The transfer of oxygen across the pulmonary blood-gas barrier depends upon its diffusion along a concentration gradient. The rate of rise of capillary partial pressure for any gas depends on the solubility ratio of the gas in the blood gas barrier (α) to that in blood (β) and its molecular weight. Oxygen, unlike inert gases, has a solubility ratio much lower than unity and thus is more susceptible to diffusion limitation. The situation is aggravated in hypoxaemia and it is the steeper slope (larger β) of the dissociation curve rather than the alveolar or venous P_{O_2} that is responsible for limitation of diffusive equilibration (Fig. 1).
2. At normal Pa_{O_2} , haemoglobin is about 95% saturated. An increase in Pa_{O_2} by breathing 100% oxygen, for example, makes little difference to the oxygen content of the blood, as only a partial pressure-dependent increase in dissolved O_2 is possible.

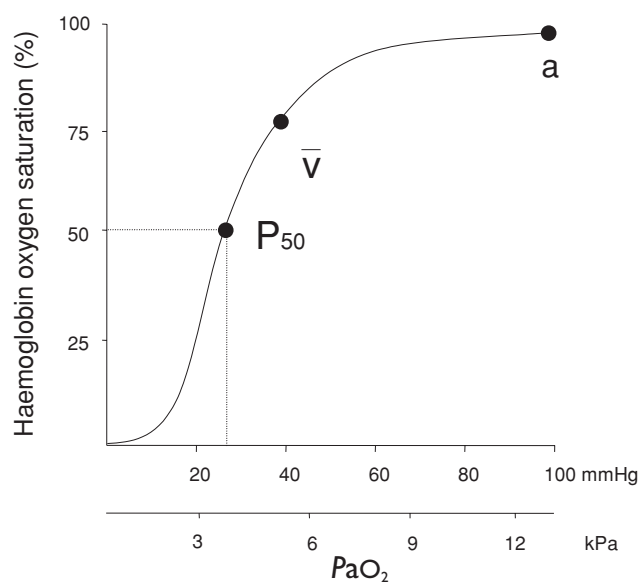


Fig. 1. The normal arterial point (a) on the oxygen-haemoglobin dissociation curve is at 95–98% saturation with a Pa_{O_2} of 100 mmHg (13.3 kPa). Mixed venous blood has a Pv_{O_2} of about 40 mmHg (5.3 kPa) and is approximately 75% saturated (v). P_{50} is defined in the text.

3. A decrease in P_{aO_2} from an initially high level has little effect on O_2 content or saturation, whereas a similar fall in P_{aO_2} in the middle range has a striking effect on oxygen content and saturation.
4. The position of the dissociation curve is defined by P_{50} – the concentration at which 50% of the haemoglobin is saturated, normally 3.5 kPa (27 mmHg). A shift in the oxygen dissociation curve to the right, as may be seen with a rise in temperature, 2,3-DPG or a fall in pH, results in decreased affinity of haemoglobin for oxygen and increased availability to body tissues.

Oxygen delivery to the tissues

Oxygen delivery to the tissues is quantified as oxygen delivery ($\dot{D}O_2$) or oxygen flux. At rest, the numerical values are (in round figures, see Eq. 3):

$$\begin{aligned} \dot{D}O_2 &= \text{Cardiac output} \times CaO_2 \\ \text{ml min}^{-1} &= 1 \text{ min}^{-1} \times \text{ml dl}^{-1} \\ 1000 &= 5.25 \times 19 \end{aligned}$$

It is clear from Equations 2 and 3 that deficiency of any of these variables would manifest as hypoxia: (i) a decrease in cardiac output (or for a particular organ, the regional blood flow) is termed as ‘stagnant hypoxia’; (ii) inadequate arterial oxygen saturation leads to ‘hypoxic hypoxia’; and (iii) failure of adequate oxygen delivery as a result of low haemoglobin is known to result in ‘anaemic hypoxia’.

The minimum value of oxygen delivery compatible with survival at rest varies with circumstances but appears to be around 300–400 ml min⁻¹. Under normal physiological conditions, the oxygen consumption ($\dot{V}O_2$) is about 250 ml min⁻¹ with an extraction ratio (OER) of ~25%. Although a derived parameter, the concept of OER is relatively simple. Ignoring the component of dissolved oxygen, it is evident that OER is independent of haemoglobin concentration.

$$\begin{aligned} \text{OER} &= \dot{V}O_2 / \dot{D}O_2 \\ &= CaO_2 - C\bar{v}O_2 / CaO_2 \\ &= \frac{[(Hb \times CO \times SaO_2) - (Hb \times CO \times S\bar{v}O_2)]}{Hb \times CO \times SaO_2} \\ &= (SaO_2 - S\bar{v}O_2) / SaO_2 \end{aligned} \tag{Eq. 4}$$

Optimum oxygen delivery

While it is inherently clear that maintenance of optimal oxygen delivery is critical for aerobic metabolism, clinical application of this concept has posed considerable challenges. Inappropriate oxygen therapy can be fatal but its prescription practices rarely meet the same standards as for other medicines. A number of

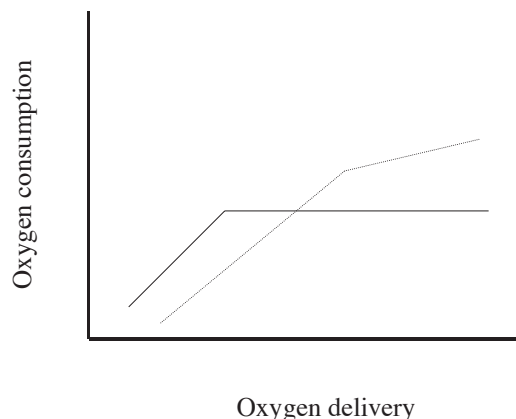


Fig. 2 For healthy subjects (solid line), oxygen delivery can be reduced without affecting oxygen consumption (supply-independent oxygenation) until the anaerobic threshold is reached. Below this, the regulation of oxygen consumption becomes dependent on oxygen delivery. A decrease in $\dot{D}O_2$ may be associated with increasing evidence of anaerobic metabolism, i.e. lactic acidosis. In sepsis (dotted line), pathological supply dependency exists – a higher $\dot{D}O_2$ is required to meet oxidative metabolic needs.

studies indicate that a lack of awareness exists about simple oxygen devices (nasal cannulae and face masks), their efficiency and delivered inspired oxygen concentrations (a complete explanation is beyond the scope of this review).

Controversy exists over improving oxygen delivery in critically ill patients. Extensions of physiological principles to the bedside to achieve therapeutic benefits have been found wanting. Several groups of investigators in the late 1980s noted that the physiological patterns of high risk postoperative patients were significantly different between the survivors and non-survivors. It was hypothesised that the observed increases in cardiac indices and $\dot{D}O_2$ seen in survivors were compensatory to improve tissue oxygenation that could be reflected by the pattern of oxygen consumption (Fig. 2). The supranormal values that were documented from survivors then provided objective physiological criteria for therapeutic goals for most of the early 1990s with disappointing results. Although maintenance of $\dot{D}O_2$ at supranormal levels may be associated with a better outcome in high risk surgical patients, augmentation of $\dot{D}O_2$ via vasoactive drugs or blood transfusions in sepsis has not resolved outcome issues.

Mechanisms of oxygen toxicity

Life and fire have intrigued mankind since evolution. Hence, experiments were performed with oxygen soon after its discovery on both combustion and respiration. According to Priestley (1775):

... as a candle burns out much faster in dephlogisticated

(oxygenated) air than in common air, so we might, as may be said, live out too fast, and the animal powers be too soon exhausted in this pure kind of air. A moralist, at least, may say, that the air which nature has provided for us is as good as we deserve.

The oxygen molecule is unique as it has 2 unpaired electrons in its outer (2P) shell in parallel orbits. This confers stability with an indefinite half-life as well as the property of paramagnetism. However, the molecule can be easily transformed into a variety of free radicals and other toxic substances that have been proposed as the cause of oxygen toxicity.

During many physiological processes, such as the reaction of xanthene with xanthene oxidase and activation of the NADPH system or in the presence of exogenous compounds like paraquat or bleomycin, oxygen is partially reduced by receiving a single electron and forms a superoxide anion ($O_2^{\bullet-}$). The superoxide anion is relatively stable at body pH and decays due to the ubiquitous presence of superoxide dismutase to yield hydrogen peroxide (H_2O_2) and eventually water (H_2O). Although both hydrogen peroxide and the superoxide anion have toxic effects, their interaction produces even more reactive species especially hydroxyl free radicals.

The main targets of oxidant attack are nucleic acids, sulphhydryl-containing enzymes, lipid peroxidation and collagen and glycoproteoglycan oxidation. At the bedside, these manifest in oxygen convulsions, pulmonary oxygen toxicity and retrolental fibroplasia. Attenuation of such injury by antioxidant therapy has not been shown to be effective and it seems that the cornerstone of avoiding the potential harmful effects of oxygen in the clinical scenario is prevention. **However, hypoxia should never be tolerated through a fear of oxygen toxicity.**

Key references

- Gilbert DL. *Oxygen and Living Processes. An Interdisciplinary Approach*, 1st edn. New York: Springer, 1981
- Nunn JF. *Nunn's Applied Respiratory Physiology*, 4th edn. Oxford: Butterworth-Heinemann, 1993
- Sibbald WJ, Mesmer K, Fink MP. Tissue oxygenation in acute medicine. In: *Update in Intensive Care and Emergency Medicine*, vol 33. Berlin: Springer, 1998
- Webster NR, Nunn JF. Molecular structure of free radicals and their importance in biological reactions. *Br J Anaesth* 1988; **60**: 98–108

See multiple choice questions 62–64.